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Die folgenden Angaben sind den vom Anmelder eingereichten Unterlagen entnommen

(54) DNA-Sequenzen für die enzymatische Synthese von Polyketid- oder Heteropolyketidverbindungen

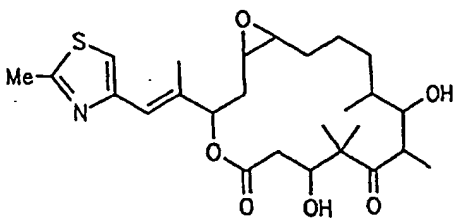
(57) Die Erfindung betrifft eine DNA-Sequenz, deren Expressionsprodukte eine enzymatische Biosynthese, Mutasynthese oder Partialsynthese von Polyketid- oder Heteropolyketitverbindungen bewirken oder daran beteiligt sind.

DE 198 46 493 A 1

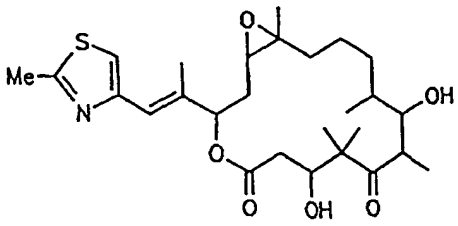
Beschreibung

Die Erfindung betrifft DNA-Sequenzen für die enzymatische Synthese von Polyketid- oder Heteropolyketidverbindungen nach Patentanspruch 1, und zwar insbesondere zur enzymatischen Synthese von Epothilonen.

Polyketid- oder Heteropolyketidverbindungen, insbesondere Epothilone, der folgenden allgemeinen Strukturformel sind beispielsweise aus DE 41 38 042, DE 196 47 580.5 und DE 197 07 501.6 bekannt:



EPOTHILON A



EPOTHILON B

worin R^1 Wasserstoff, C_{1-4}-Alkyl, C_{1-4}-Acyl, Li^+, K^+, Na^+, $^1/_2\ Mg^{2+}$ oder $^1/_2\ Ca^{2+}$ bedeutet und R^2 Wasserstoff oder eine Methylgruppe darstellt.

Die Epothilone werden in die Typen A bis F eingeteilt. Sie haben cytotoxische und/oder immunsupressive sowie antibiotische und antifungale Wirkungen und finden daher zum Beispiel Anwendung als Mittel für den Pflanzenschutz in Landwirtschaft, Forstwirtschaft und/oder im Gartenbau.

Die Epothilone wurden bisher fermentativ durch Kultivierung von Sporangium-Stämmen hergestellt und durch Anwendung herkömmlicher Techniken isoliert und gereinigt, vgl. z. B. DE 41 38 042.8.

Fermentative Techniken sind aber oft mit Nachteilen verbunden. Der produzierende Mikroorganismus erlaubt nicht in jedem Fall die fermentative Herstellung in großem Maßstab. Häufig kommt es zu Komplikationen bei der großmaßstäblichen Kultivierung oder die Ausbeuten sind gering oder die Isolierung und Reinigung sind aufwendig.

Daher wäre es vorteilhaft, wenn zur fermentativen Herstellung der gewünschten Verbindungen ein gut charakterisierter und leicht zu handhabender Mikroorganismus zur Verfügung stünde. Wenn ein solcher aber nicht in der Natur gefunden oder gezüchtet werden kann, bleibt nur noch die entsprechende Veränderung eines geeigneten Mikroorganismus mit gentechnischen Methoden. Dazu ist aber die Isolierung und Charakterisierung der entsprechenden Gene erforderlich.

Aufgabe der Erfindung ist daher gemäß Patentanspruch 1 die Bereitstellung einer DNA-Sequenz, deren Expressionsprodukte die enzymatische Biosynthese, Mutasynthese oder Partialsynthese von Polyketid- oder Heteropolyketidverbindungen bewirken oder daran beteiligt sind.

Durch die Bereitstellung einer derartigen DNA-Sequenz lassen sich folgende Vorteile erzielen.

Die DNA-Sequenz läßt sich mit üblichen molekularbiologischen Methoden in bekannte und optimierte Expressionsvektoren insertieren, wodurch die entsprechende Transformation, Selektion und Klonierung von Zellen möglich ist, die dann zur Synthese von Polyketid- oder Heteropolyketidverbindungen durch Fermentation in der Lage sind. Wenn ein überproduzierender Zellklon gewählt wird, lassen sich die gewünschten Polyketid- oder Heteropolyketidverbindungen leicht in großen Mengen herstellen und gewinnen.

Die Kenntnis der Lage der regulatorischen DNA-Abschnitte und der einzelnen Strukturgene gestattet die gezielte Mutagenese ("site-directed mutagenesis") mit üblichen gentechnischen Methoden und somit die Konstruktion von optimierten Enzymen ("protein engineering") zur fermentativen Synthese von Polyketid- oder Heteropolyketidverbindungen.

Die Erfindung betrifft somit ferner einen rekombinierten Expressionsvektor nach Patentanspruch 8, damit transformierte Zellen nach Patentanspruch 9 sowie ein Verfahren zur enzymatischen Biosynthese, Mutasynthese oder Partialsynthese von Polyketid- oder Heteropolyketidverbindungen nach Patentanspruch 15.

Vorteilhafte Ausführungsformen der Erfindung sind Gegenstand der Unteransprüche.

Die Erfindung wird nachstehend detaillierter erläutert.

Fig. 1 ist eine Restriktionskarte der erfindungsgemäßen DNA-Sequenz, die auch die Lage der regulatorischen DNA-Abschnitte und der einzelnen Strukturgene ("open reading frames" (ORF) 1 bis 14) angibt.

Fig. 2 ordnet den ORF 1 bis 14 die jeweilige biologischen Funktion (Regulatoren, Enzyme) zu.

Isolation und Charakterisierung der DNA-Sequenz

Es wurde genomische DNA aus dem Myxobakterium Sorangium cellulosum Soce90, Stamm und Anzucht bekannt aus DE 41 38 042, verwendet.

Genomische DNA wurde mit Hilfe des Qiagen Blood & Cell Culture DNA Kits (Qiagen, Hilden, FRG) isoliert. Siehe dazu "Genomic DNA handbook" S. 31 ff (Qiagen 1995). Modifizierungen: Nach Denaturierung und Proteolyse wurde eine Phenol-Chloroformextraktion, gefolgt von einer Ethanolpräzipitation, vorgenommen (Sambrook J., Fritsch E. F., Maniatis T., Molecular Cloning, A Laboratory Manual, Cold Spring Harbour Laboratory Press, New York; 1989). Die in Puffer gelöste DNA wurde anschließend auf die Qiagen-Reinigungssäulen aufgetragen und gemäß den Herstellerangaben isoliert.

Konstruktion von geeigneten rekombinierten Expressionsvektoren

Expression in Myxobakterien

Eine heterologe Expression der in **Fig.** 1 aufgeführten ORFs wird unter Verwendung eines Derivats des Plasmids pSUP102 (Simon R., Priefer U., Pühler A.; Methods in Enzymol, 118: 643–659; 1986), bei welchem das Chloramphenicolresistenzgen durch eine Streptomycinresistenzgenkassette mit Promotorelement aus dem Transposon TNS ausgetauscht wurde, ausgeführt. Homologe kurze Abschnitte genomischer DNA aus dem Wirtsorganismus werden mit den DNA-Sequenzen entsprechend **Fig.** 1 unter Benutzung effektiver Regulationselemente in z. B. die Restriktionsschnittstelle EcoRI des Vektors ligiert. Nach Amplifikation des Vektors in Escherichia coli erfolgt der Transfer der. DNA durch Elektroporation der Wirtszellen oder durch Konjugation mit Escherichia coli S17-I (Simon R., Priefer U., Pühler A., Bio/Technology 1: 784–791; 1983).

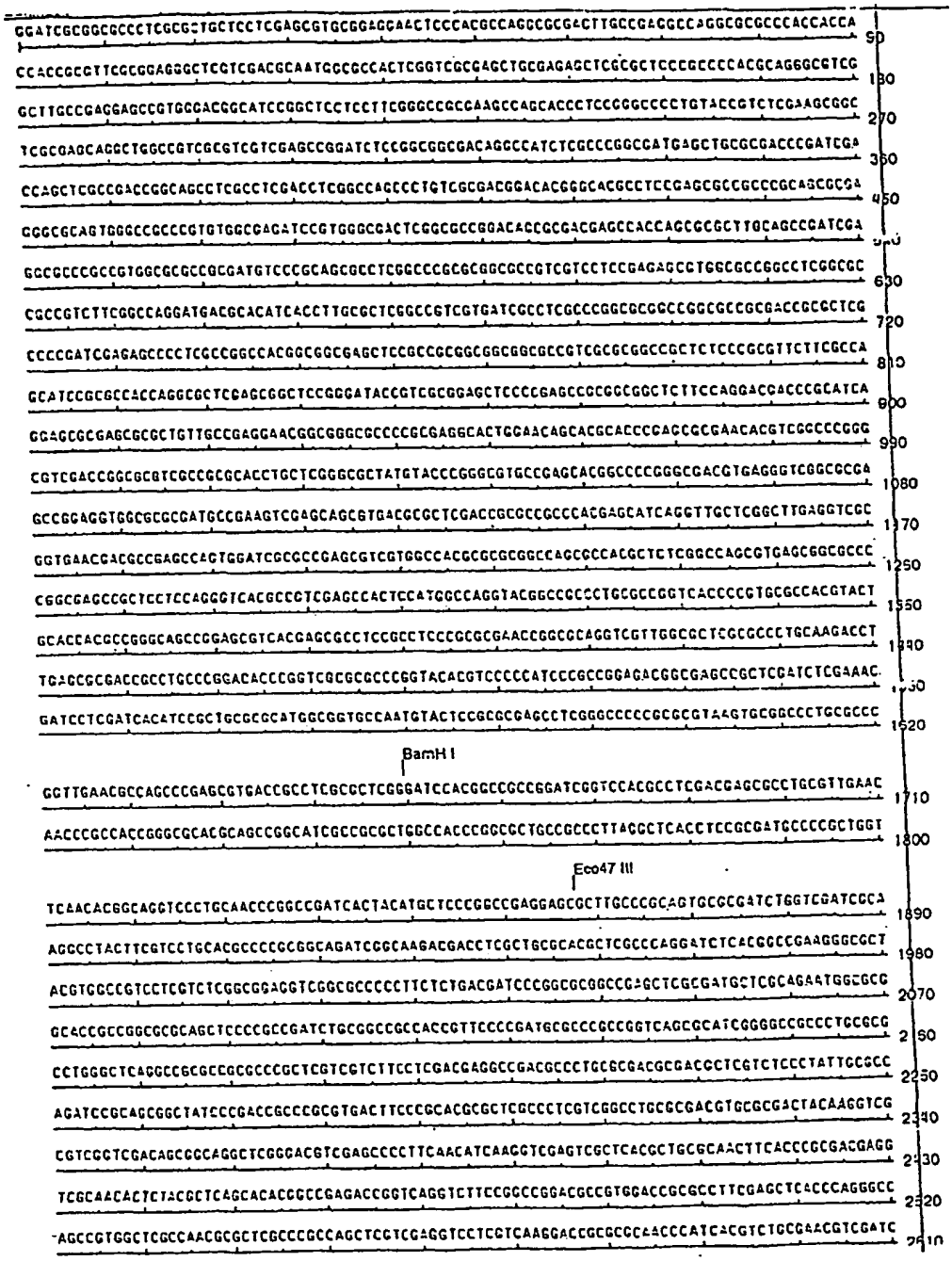
Mit Hilfe der durch den Vektor vermittelten Tetrazyklin- bzw. Streptomycinresistenz werden die Wirtszellen auf Integration der rekombinanten Plasmid-DNA durch homologe Rekombination in das Chromosom überprüft.

Expression in Zellen von Streptomyces

Eine heterologe Expression der in **Fig.** 1 aufgeführten ORFs wird unter Verwendung der bifunktionalen Streptomyces-Escherichia coli-Cosmide pKU206 oder pOJ466 vorgenommen.

Expression von Zellen in Escherichia coli

Eine heterologe Expression der in **Fig.** 1 aufgeführten ORFs wird unter Verwendung von "Bacterial Artificial Chromosomes", Cosmiden (z. B. Supercos; Stratagene GmbH, Heidelberg) und T7-Expressionssystemen (Stratagene GmbH, Heidelberg; New England Biolabs GmbH, Schwalbach, FRG) vorgenommen. Die Expression rekombinierter Enzyme erfolgt in Escherichia coli-Zellen, die eine konstitutive Expression einer Phosphopantetheinyl-Transferase gewährleisten, welche für die Bildung von Holoenzym-Polyketidsynthasen und -Polypeptidsynthetasen notwendig ist.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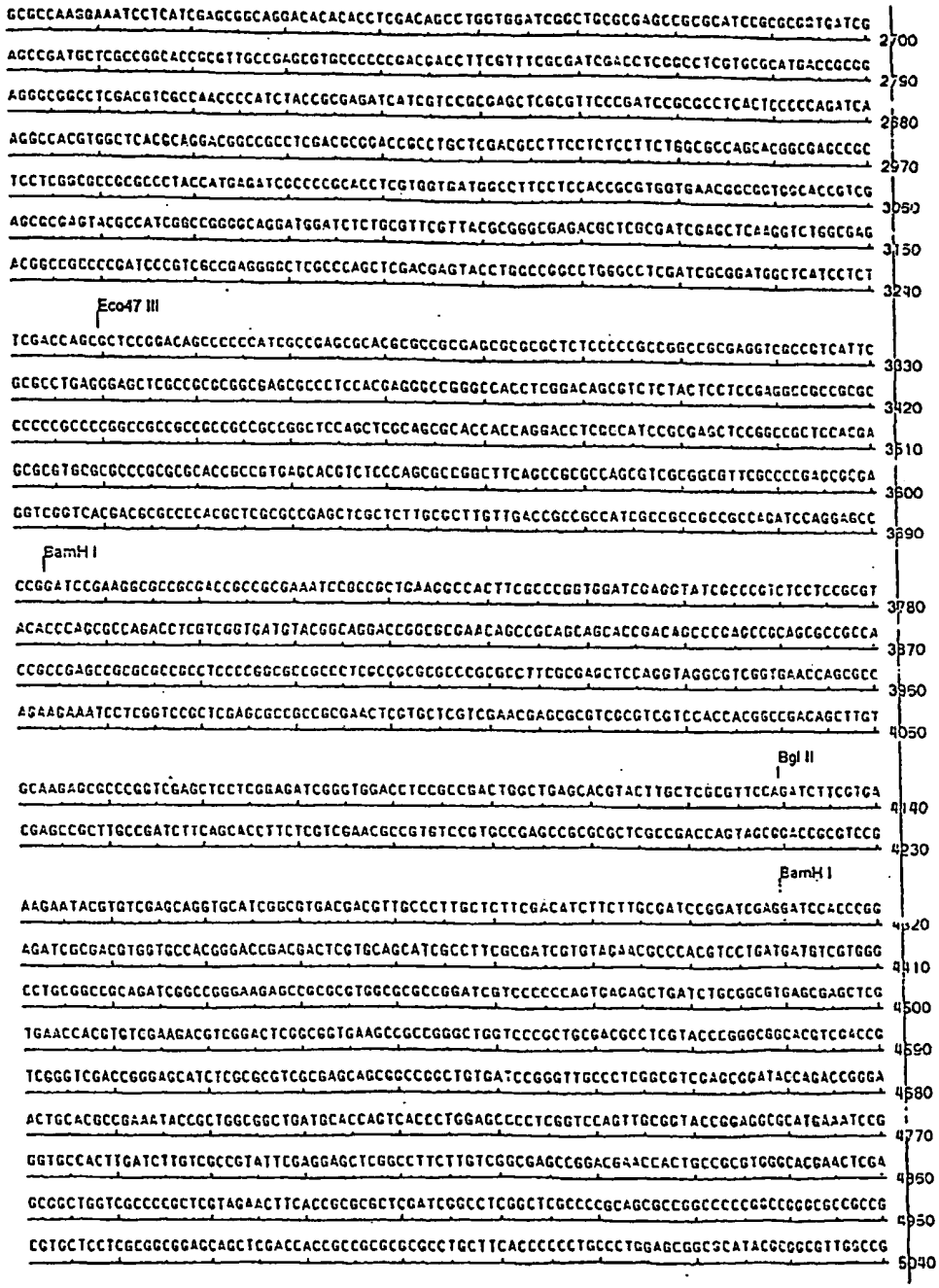
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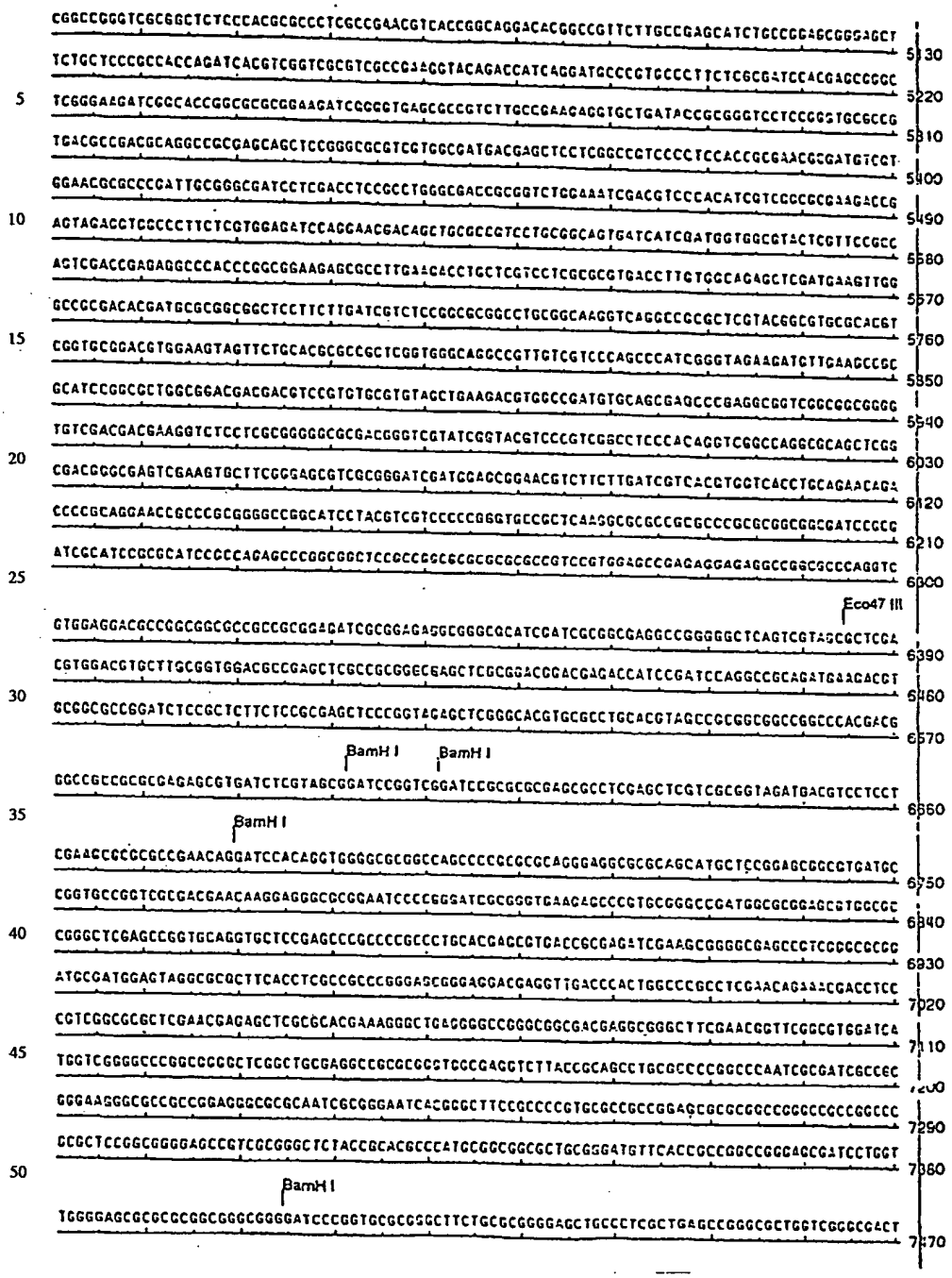
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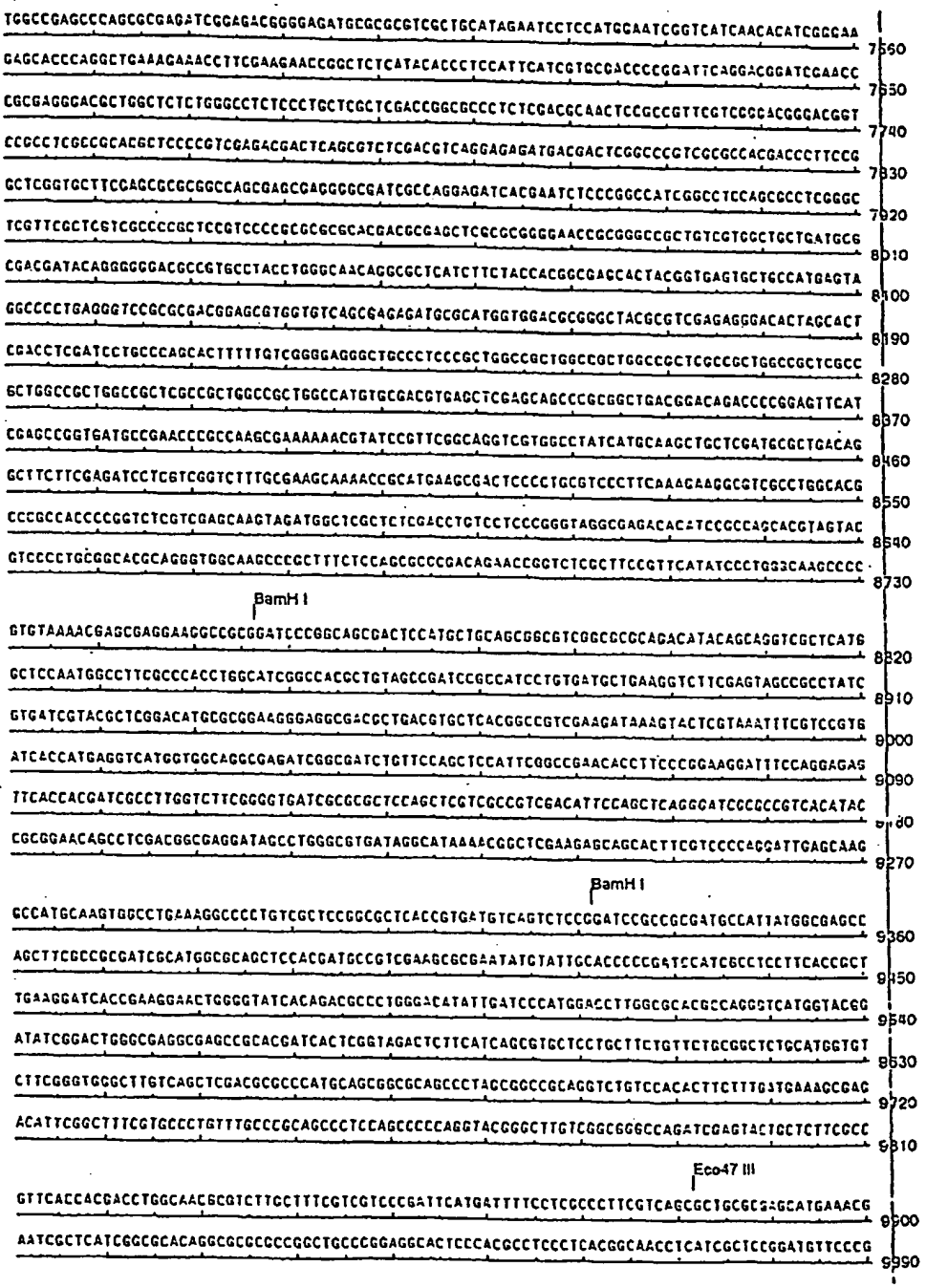
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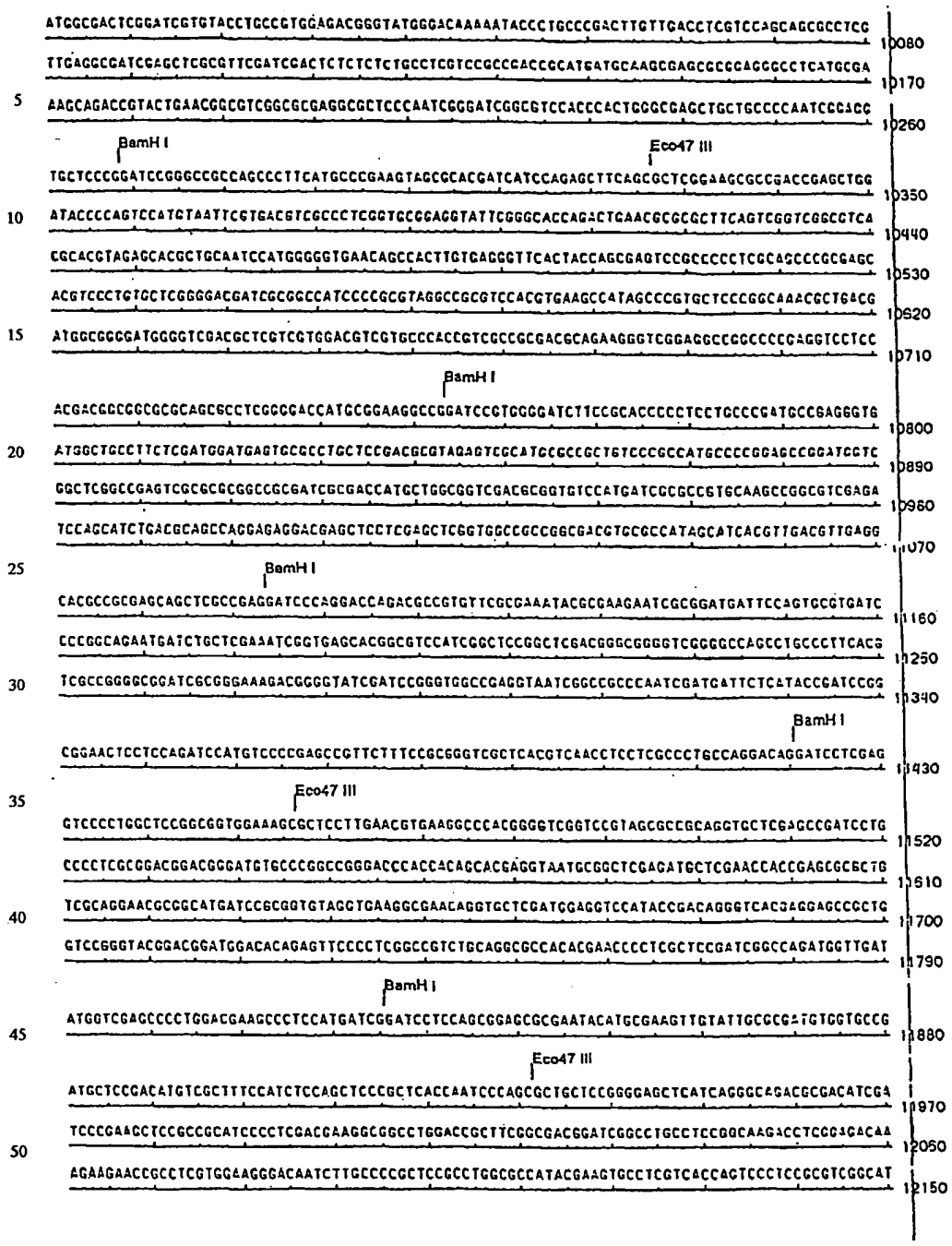
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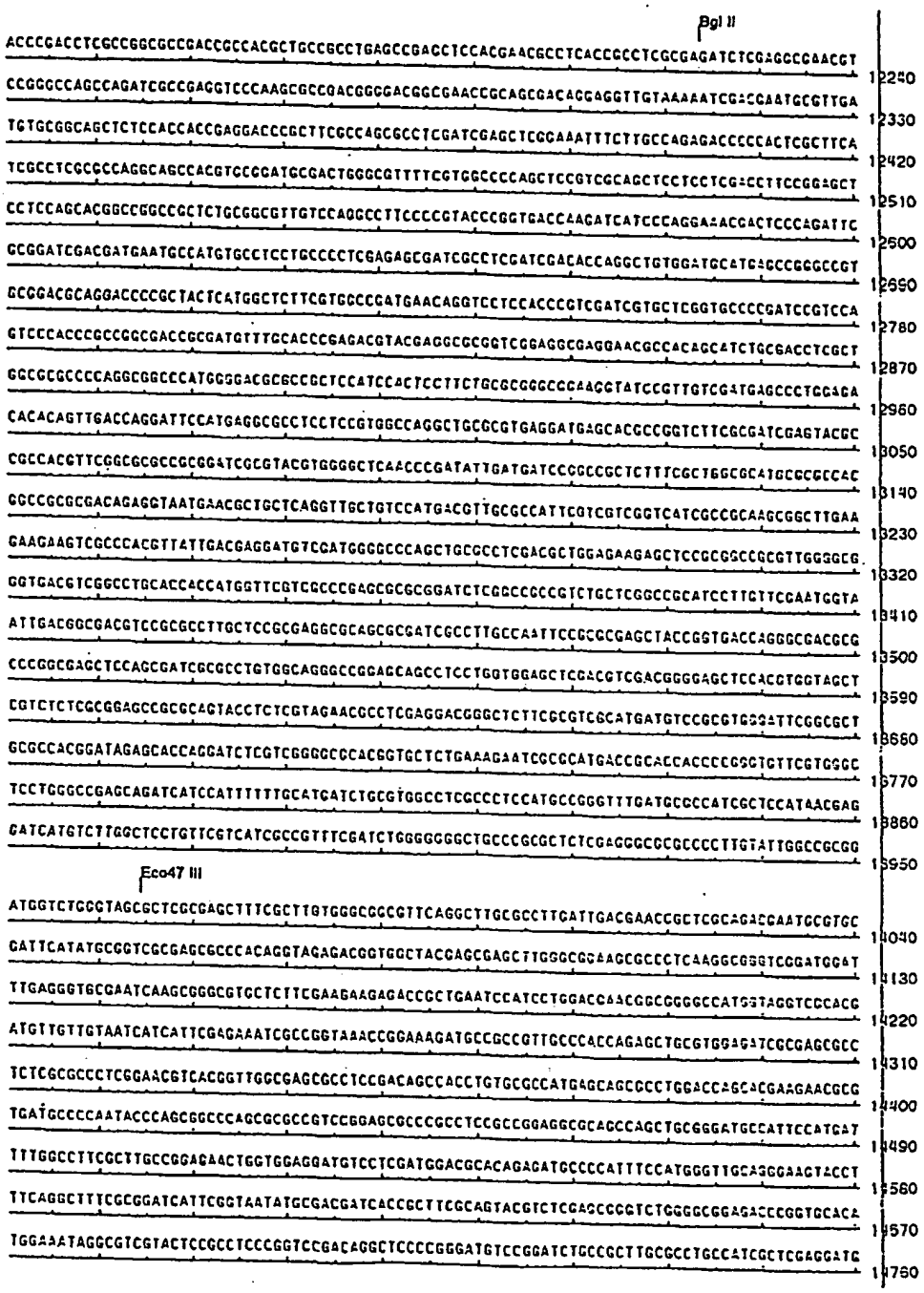
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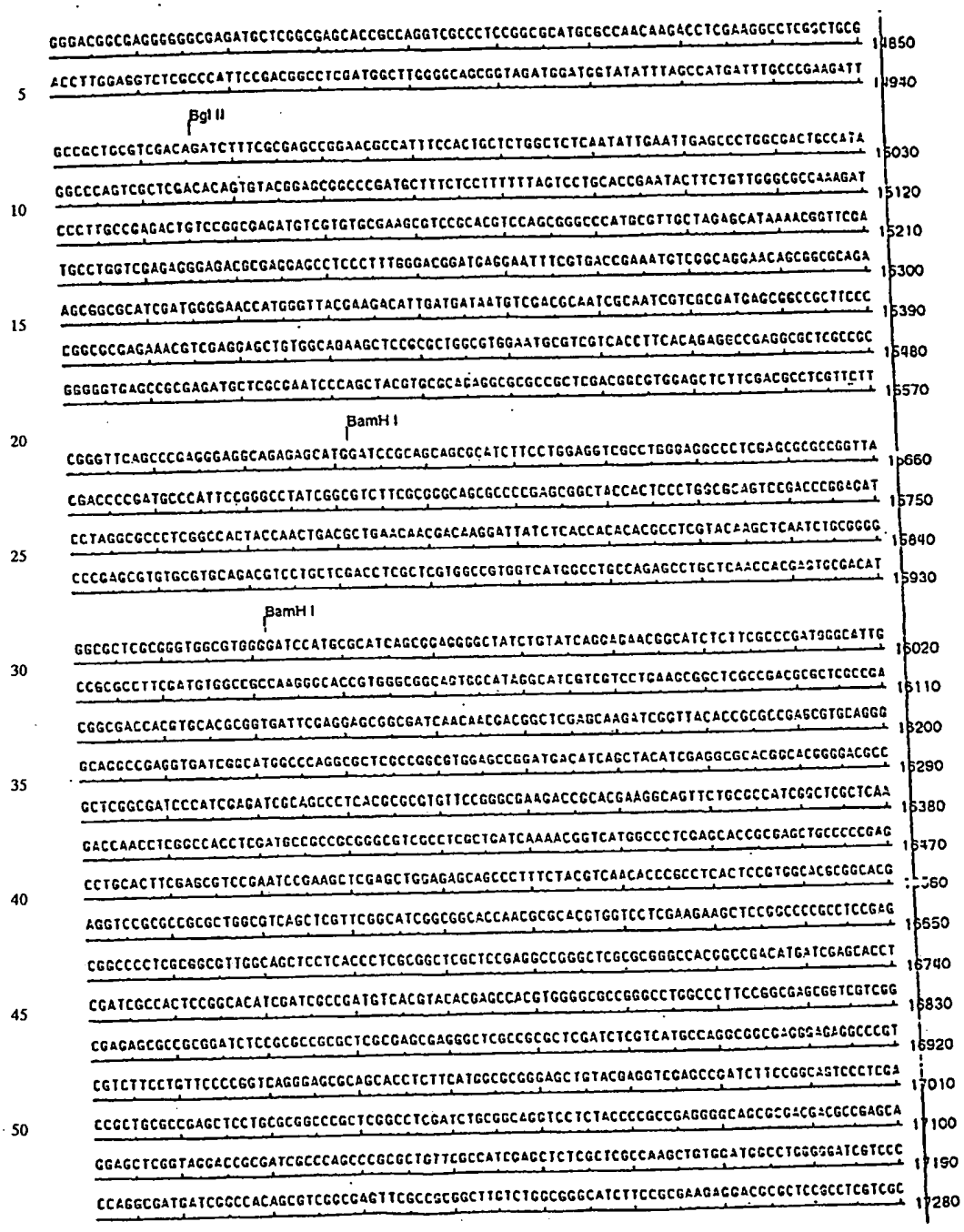
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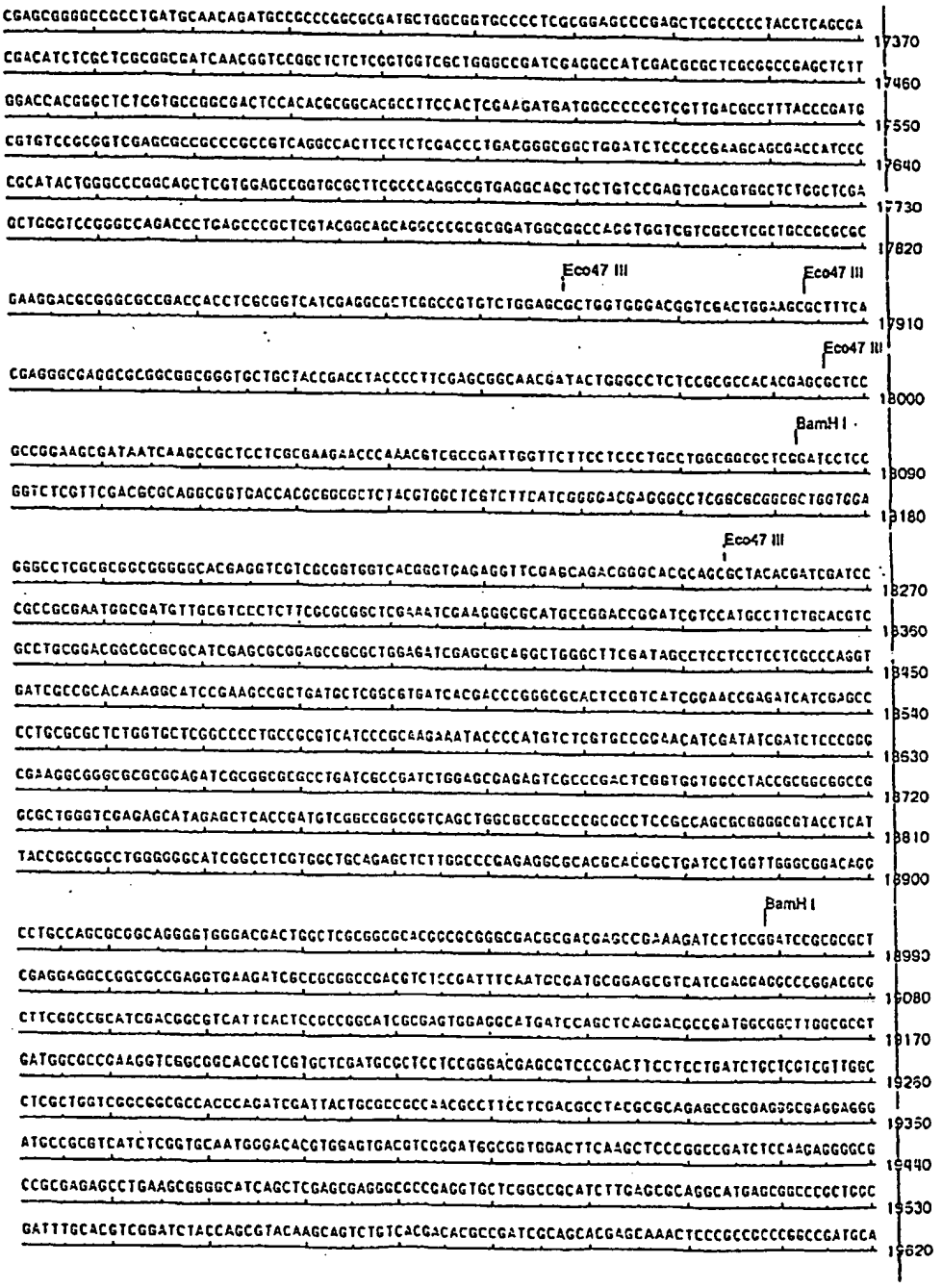
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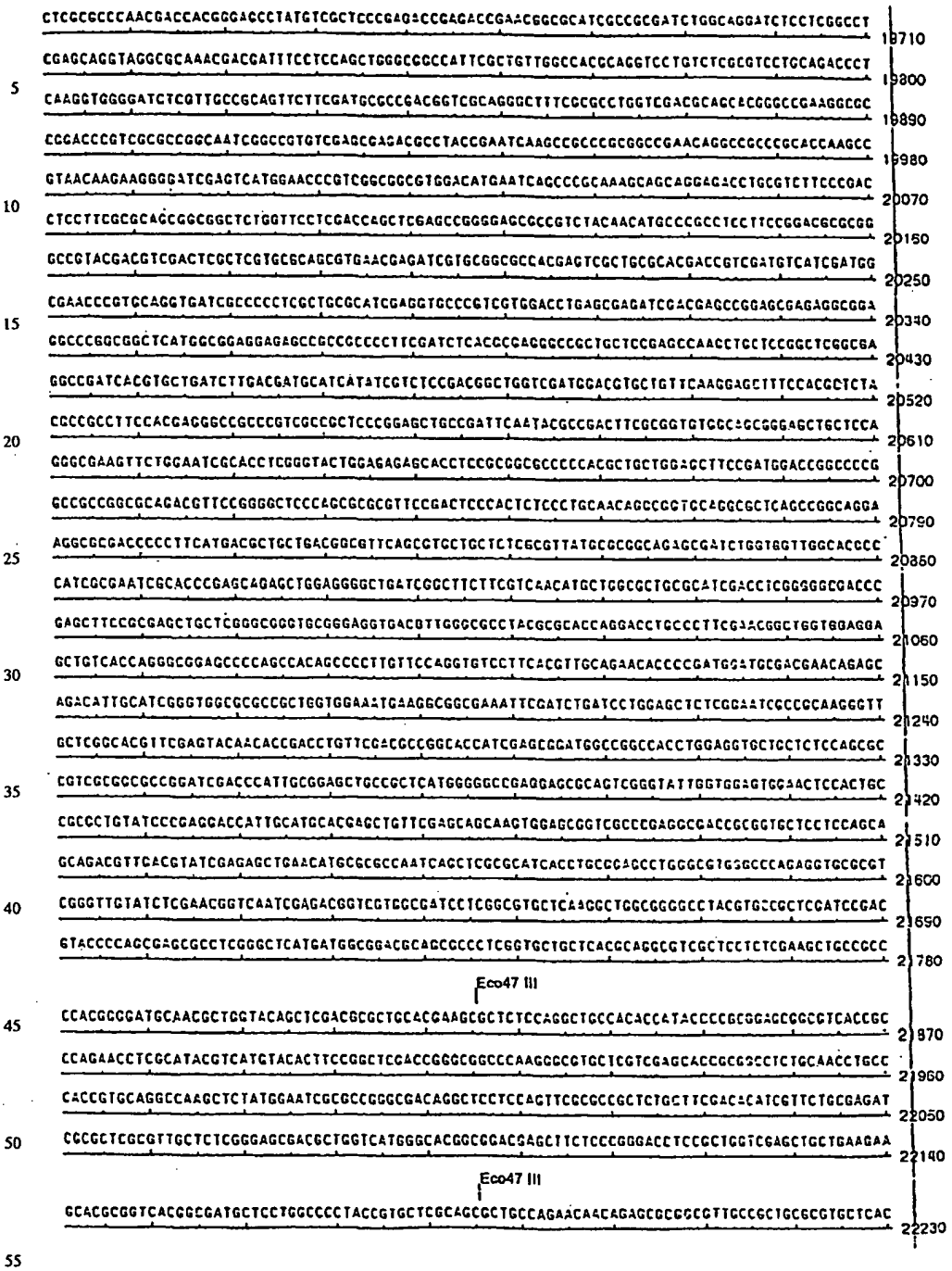
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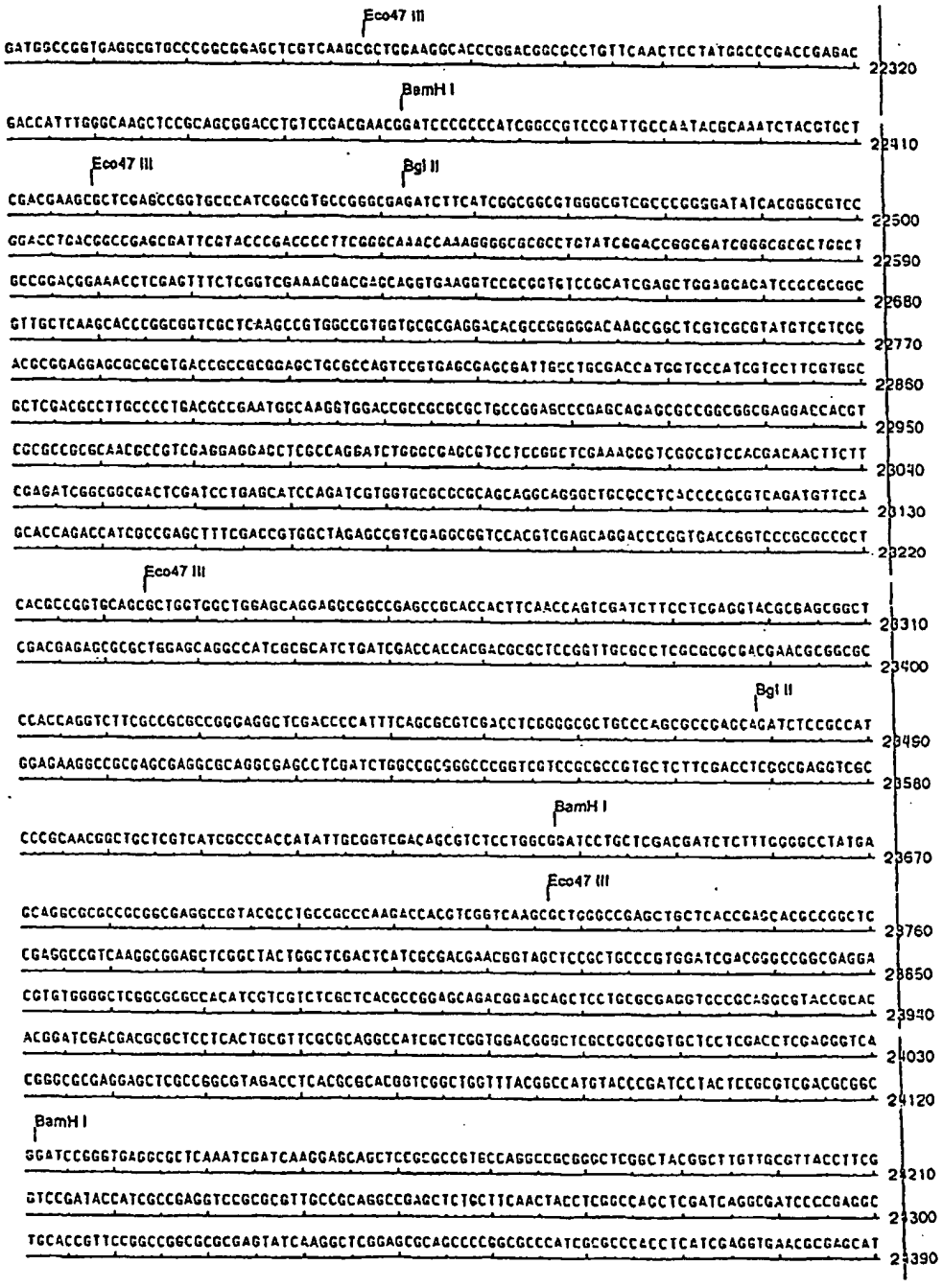
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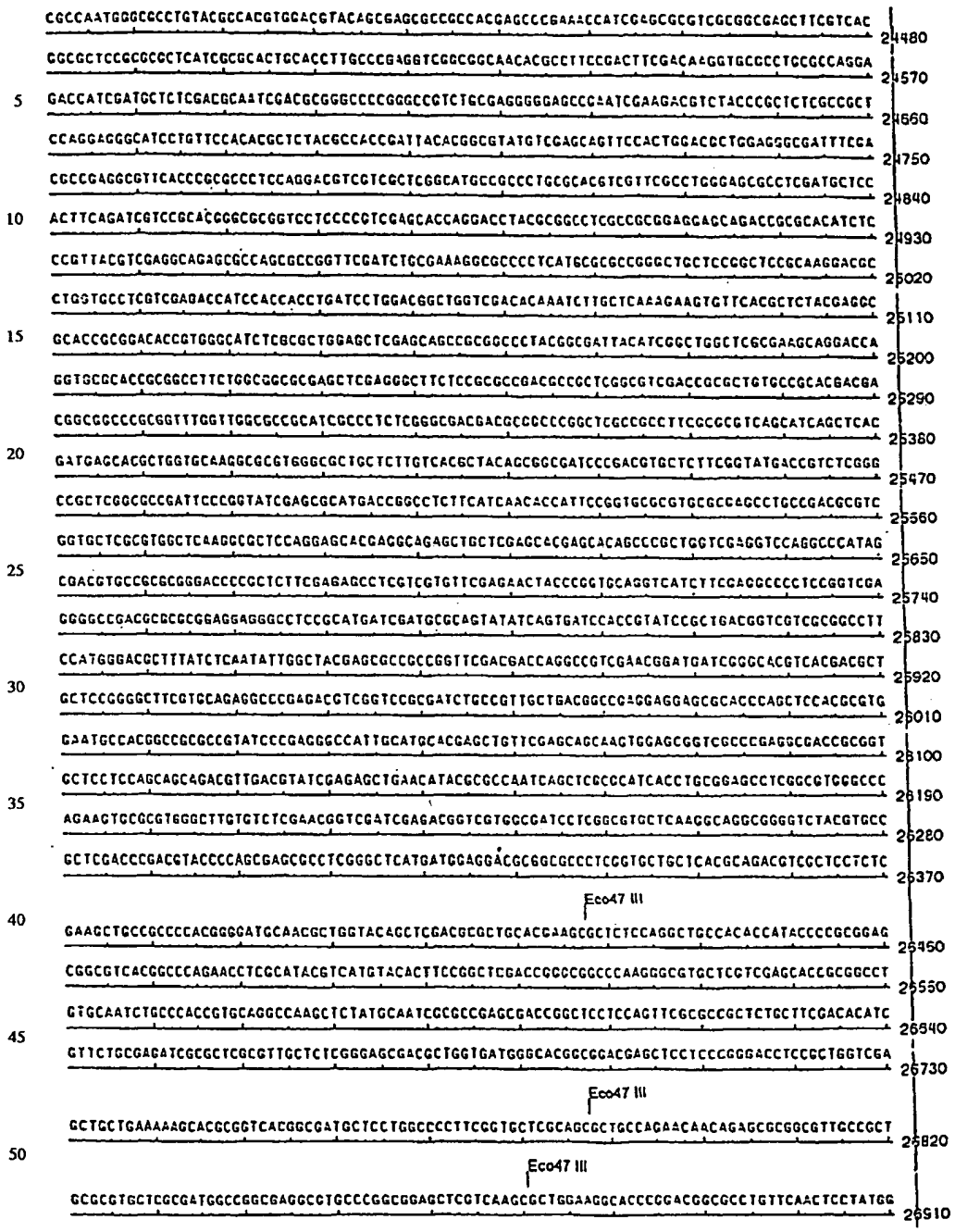
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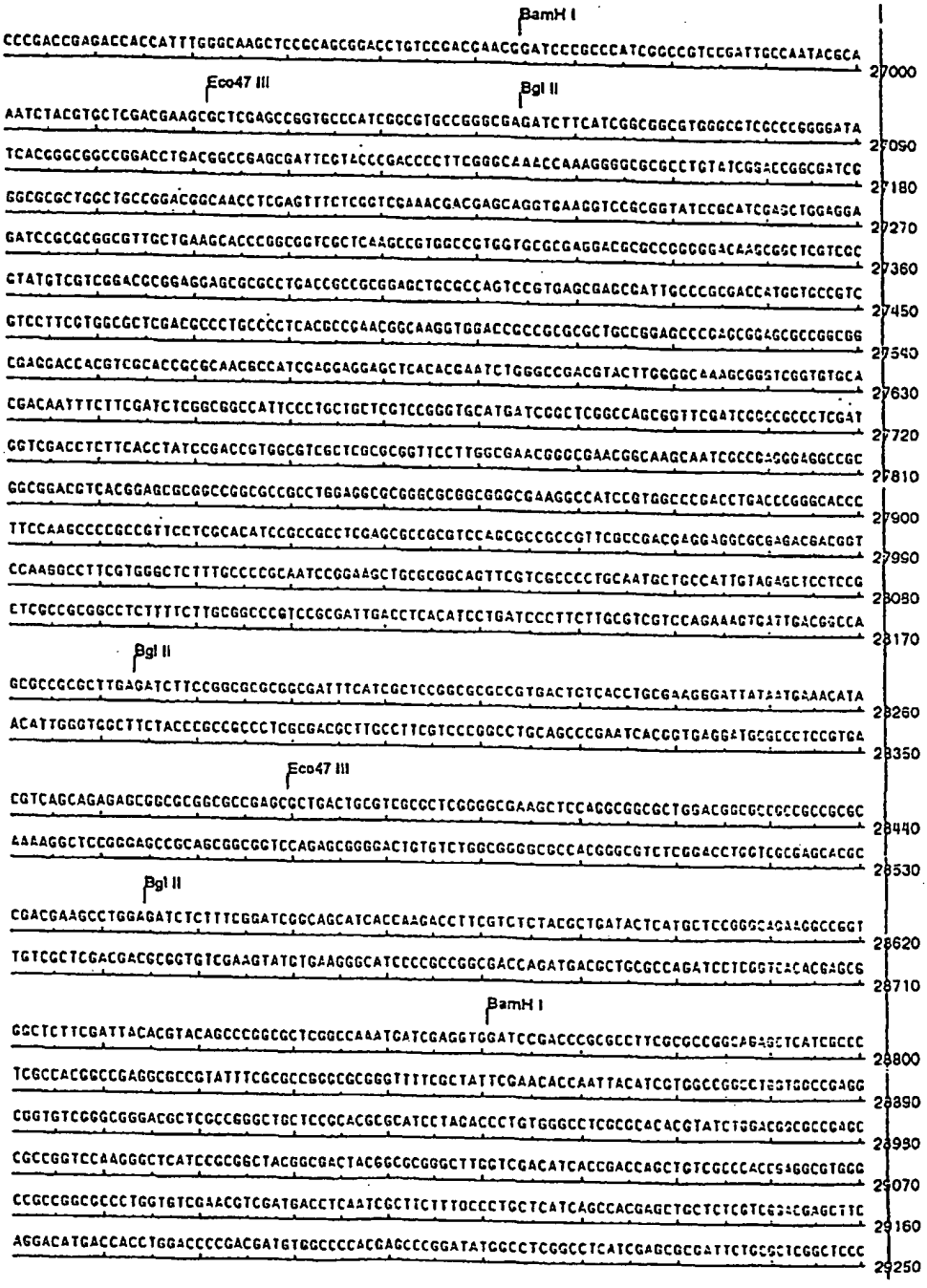
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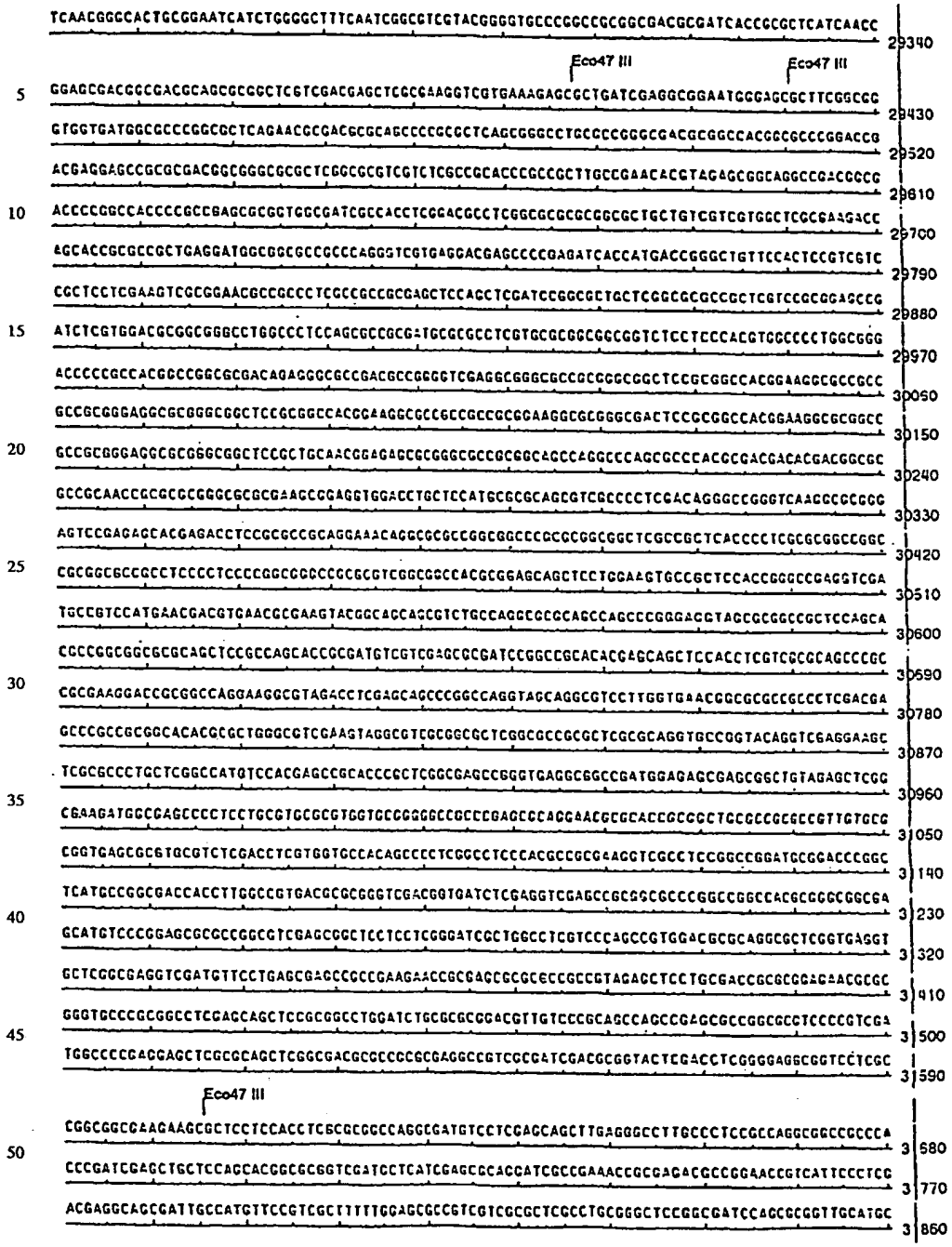
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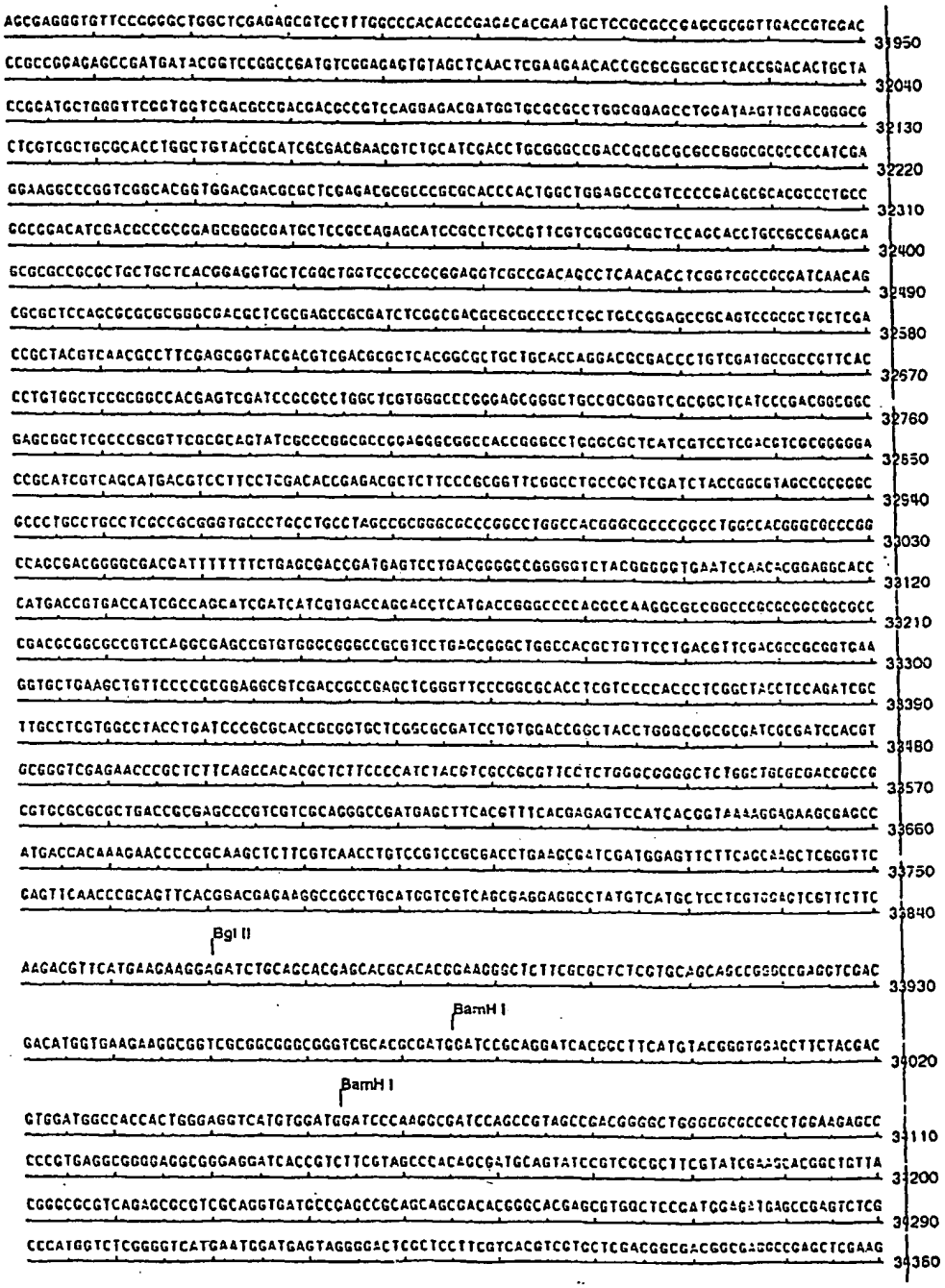
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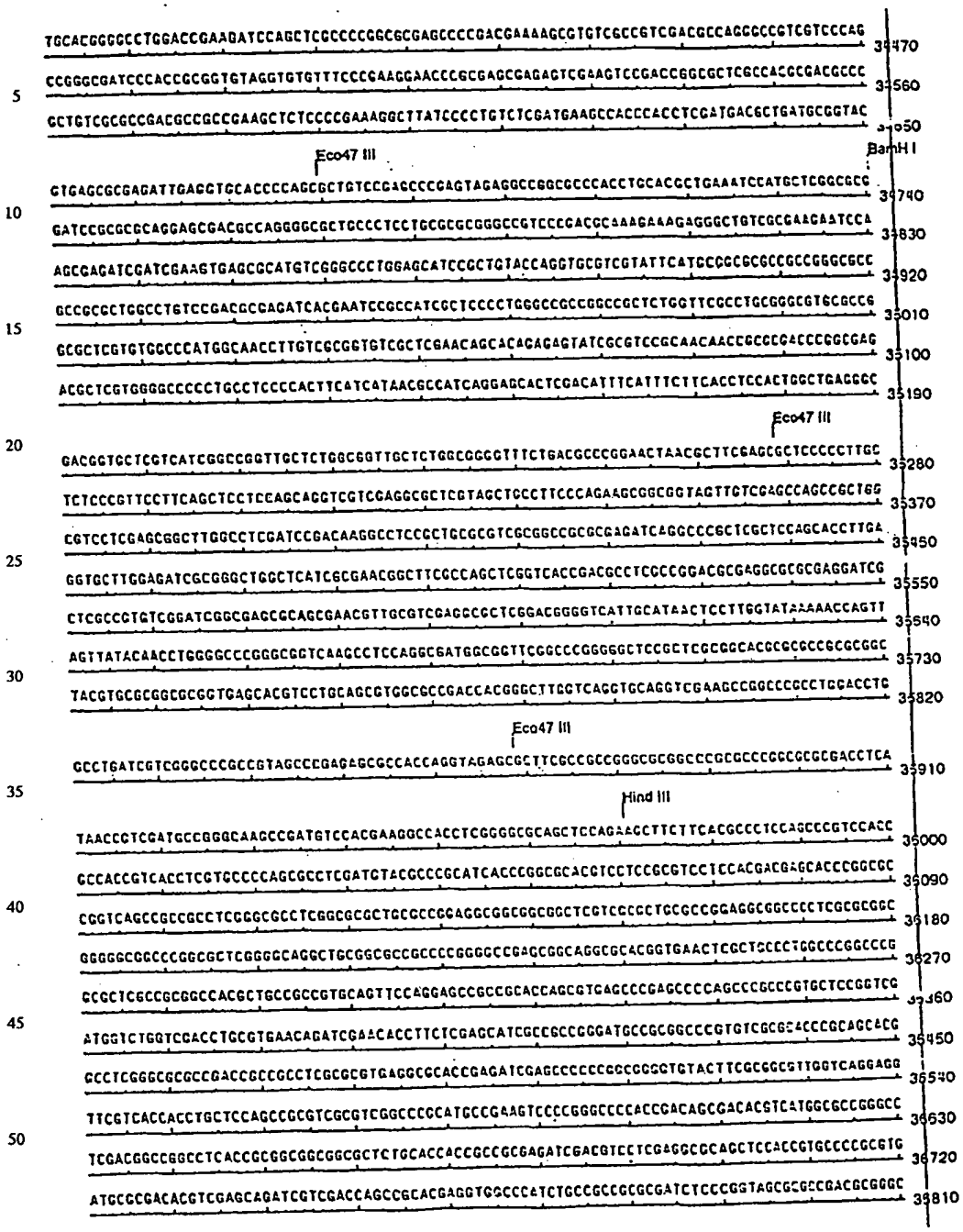
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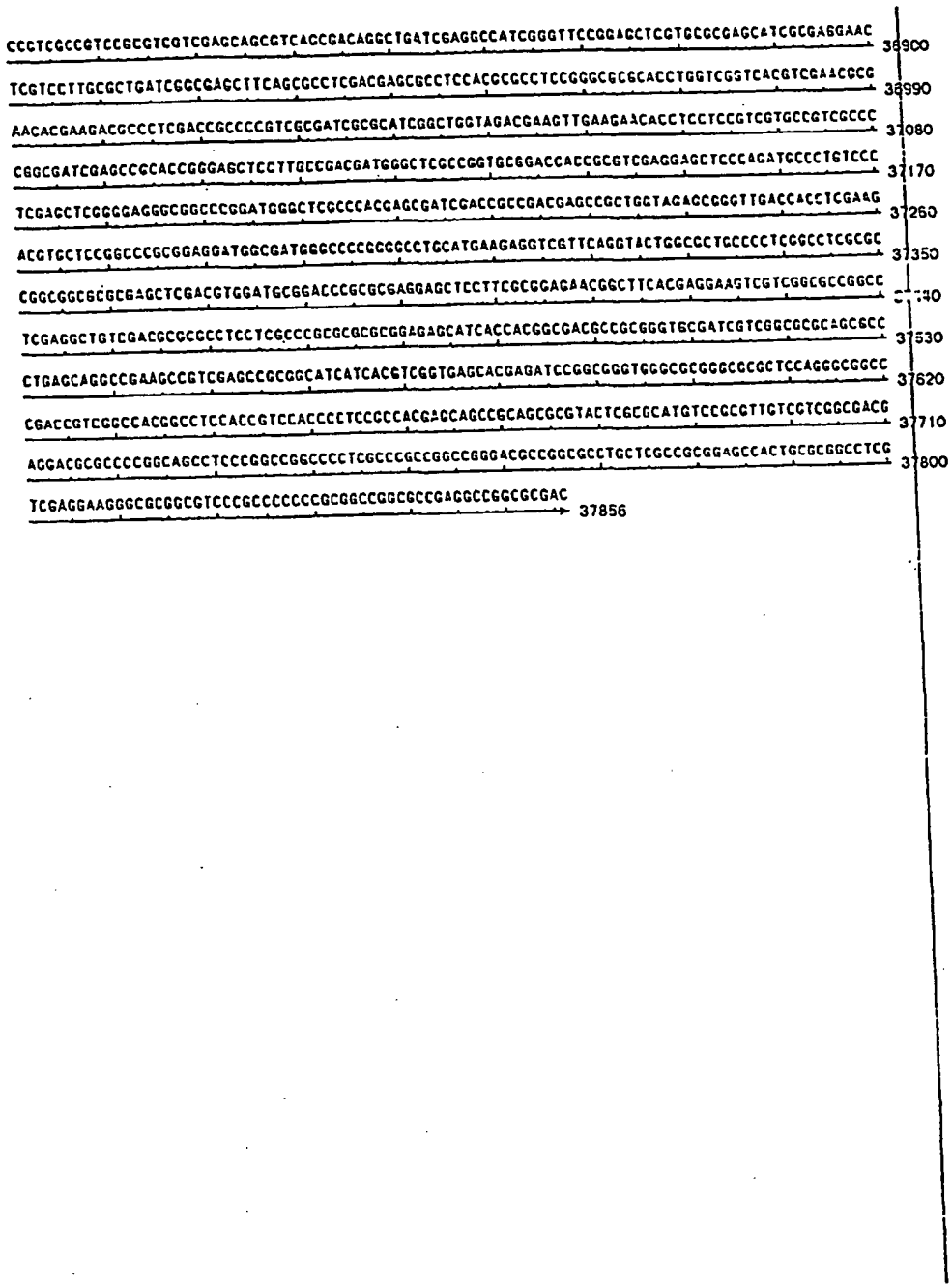
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Patentansprüche

1. DNA-Sequenz, deren Expressionsprodukte die enzymatische Biosynthese, Mutasynthese oder Partialsynthese von Polyketid- oder Heteropolyketidverbindungen bewirken oder daran beteiligt sind.
2. DNA-Sequenz nach Anspruch 1, wobei es sich bei den Polyketid- oder Heteropolyketidverbindungen um Epothilone handelt.
3. DNA-Sequenz nach einem der vorhergehenden Ansprüche, wobei die DNA-Sequenz Regulationselemente (ORF9, ORF11 und ORF12) und Transkriptionsregulatoren (ORF10, ORF13 und ORF14) aufweist und die Expressionsprodute eine tRNA-Synthetase (ORF1), Monooxygenase (ORF2), Aminotransferase (ORF3), Tyrosin/DOPA-Decarboxylase (ORF4), 3-Oxoacyl-ACP-Reduktase (ORF5), Polyketidsynthase (ORF6), Peptidsynthetase (ORF7) und Transpeptidase (ORF8) umfassen.
4. DNA-Sequenz nach einem der vorhergehenden Ansprliche, wobei die DNA aus Myxobakterien stammt.
5. DNA-Sequenz nach einem der vorhergehenden Ansprüche, wobei die DNA aus Sorangium-Stämmen stammt.
6. DNA-Sequenz nach einem der vorhergehenden Ansprliche, wobei die DNA aus Sorangium cellulosum stammt.
7. DNA-Sequenz nach einem der vorhergehenden Ansprüche, wobei die DNA ausgewählt ist unter:
   (a) der folgenden DNA-Sequenz: oder deren komplementärem Strang,
   (b) DNA-Sequenzen, die unter stringenten Bedingungen an die Proteine kodierenden Regionen der in (a) definierten DNA-Sequenzen oder an Fragmente davon hybridisieren,
   (c) DNA - Sequenzen, die wegen der Degeneration des genetischen Kodes an die unter (a) und (b) definierten DNA-Sequenzen hybridisieren,
   (d) alle Variationen und durch Substitution, Insertion oder Deletion von Nucleotiden entstandene Mutanten der unter (a) bis (c) definierten DNA-Sequenzen, die isofunktionelle Expressionsprodukte ergeben.
8. Rekombinierter Expressionsvektor, der eine DNA-Sequenz nach einem der Ansprüche 1–7 enthält.
9. Prokaryotische oder eukaryotische Zelle, die mit einer DNA-Sequenz nach einem der Ansprüche 1 bis 7 oder mit einem rekombinierten Expressionsvektor nach Anspruch 8 transformiert oder transfiziert ist.
10. Zelle nach Anspruch 9, wobei die Zelle von Myxobakterien stammt.

11. Zelle nach Anspruch 9, wobei die Zelle von einem Sorangium-Stamm stammt.
12. Zelle nach Anspruch 9, wobei die Zelle von Sorangium cellulosum stammt.
13. Zelle nach Anspruch 9, wobei die Zelle von einem Streptomyces-Stamm stammt.
14. Zelle nach Anspruch 9, wobei die Zelle von Escherichia coli stammt.
15. Verfahren zur enzymatischen Biosynthese, Mutasynthese oder Partialsynthese von Polyketid- oder Heteropolyketidverbindungen, bei dem eine Zelle nach einem der Ansprüche 9 bis 14 in einem geeigneten Kulturmedium kultiviert und die Polyketid- oder Heteropolyketidverbindung aus dem Medium isoliert wird.
16. Verfahren nach Anspruch 15, wobei die Polyketid- oder Heteropolyketidverbindung ein Epothilon ist.

Hierzu 2 Seite(n) Zeichnungen

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Fig. 1

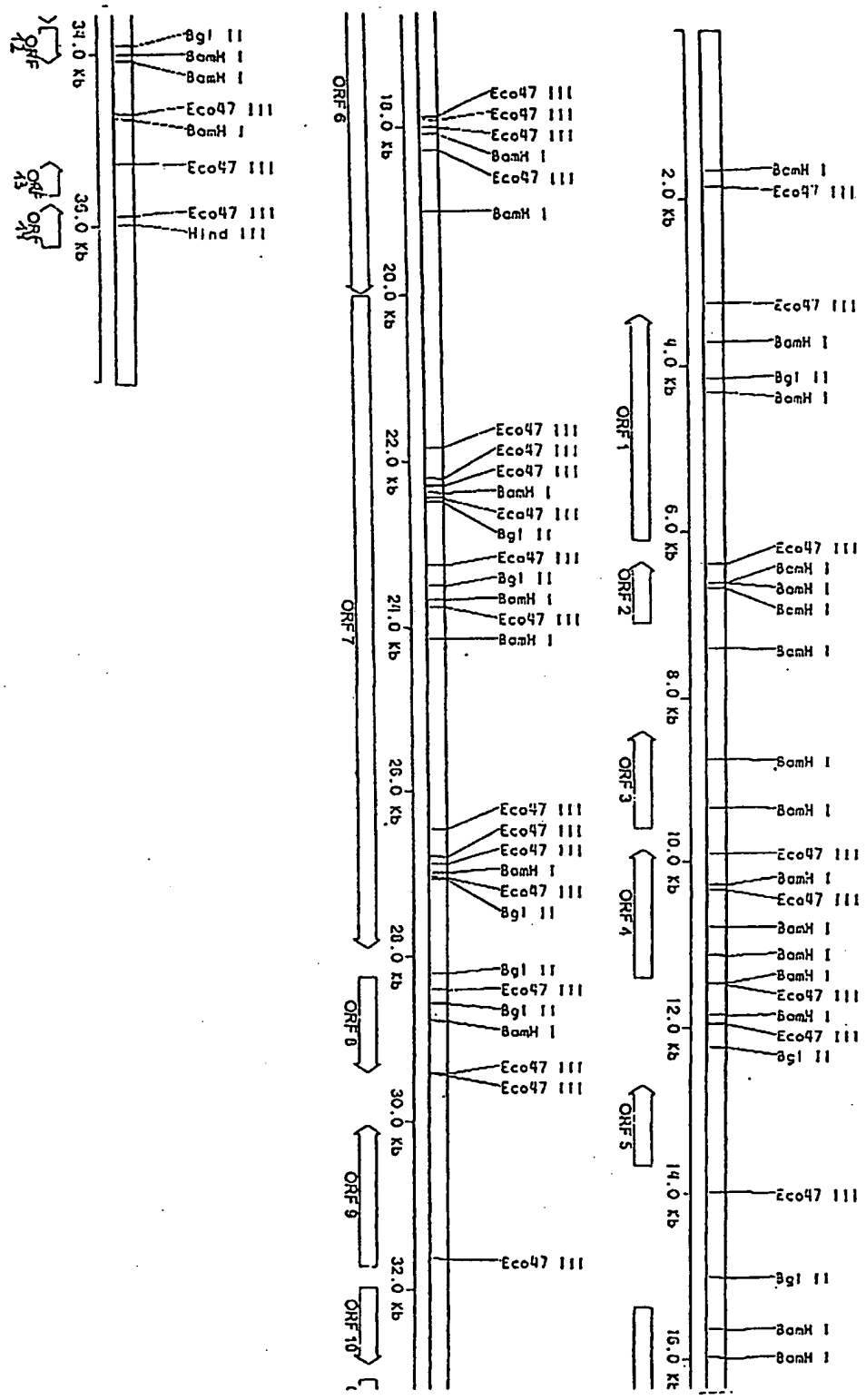

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Fig. 2

	Gen/Funktion	Position
ORF 1	tRNA-Synthetase	6100-3397
ORF 2	Monooxygenase	7111-6374
ORF 3	Aminotransferase	9550-8433
ORF 4	Tyrosin/DOPA-Decarboxylase	11393-9854
ORF 5	3-Oxoacyl-ACP-Reduktase	12212-13656
ORF 6	Polyketidsynthase	15374-19984
ORF 7	Peptidsynthetase	20003-27889
ORF 8	Transpeptidase	28251-29402
ORF 9	Regulationselement	31720-30040
ORF 10	Transkriptionsregulator	31982-32932
ORF 11	Regulationselement	33128-33613
ORF 12	Regulationselement	33661-34076
ORF 13	Transkriptionsregulator	35616-35255
ORF 14	Transkriptionsregulator	36242-35730